

Glycoprotein-Complex or Hybrid N-glycans

The diagram illustrates the biosynthesis of various glycoprotein complexes and hybrid N-glycans through several enzymatic pathways:

- Initial Structure:** A complex branched structure featuring multiple mannose (Man) residues linked via $\alpha 1,2$, $\alpha 1,3$, and $\alpha 1,6$ bonds. It also includes glucose (Glc), galactose (Gal), fucose (Fuc), and sialic acid (Sia) components.
- Enzymatic Pathways:**
 - glycosidases:** Enzymes responsible for the removal of specific sugar residues.
 - I. hydrolytic enzymes (as necessary) (ie. mannosidases, phosphatases, galactosidases, etc.):** These enzymes facilitate the conversion of the initial structure into simpler forms like HIGH MANNOSE or more complex ones like WSP (Water Soluble Polysaccharide).
 - GNT-1, GNT-1 and 2, GNT-1; Gal Transferase, GNT-1; GNT-2; Gal transferase, GNT-1; GNT-2; Gal transferase; sialyltransferase:** These enzymes are involved in the addition and modification of specific sugars, leading to the formation of structures like WSP, SA (Sialic Acid), and Gal (Galactose).
 - sialyltransferase(s):** Enzymes responsible for adding sialic acid residues to the glycan chains.
- Final Products:** The pathways lead to various glycoprotein complexes and hybrid N-glycans, including those labeled "HIGH MANNOSE", "WSP", "SA", "Gal", and "GlcNAc".

R = H, Glc, Man, mannose, galactomannan, polysaccharide, polyisaccharide-phosphate, Man-phosphate.
S = H, phosphate, mannose-phosphate, mannan-phosphate.
Sugar = H, xylose, GlcNAc, Man.
a = 0, or 1; b = 0 or 1; c = 0, 1.
WSP = water soluble polymer (ie. PEG, etc.), toxin, chelating agent, or peptide.

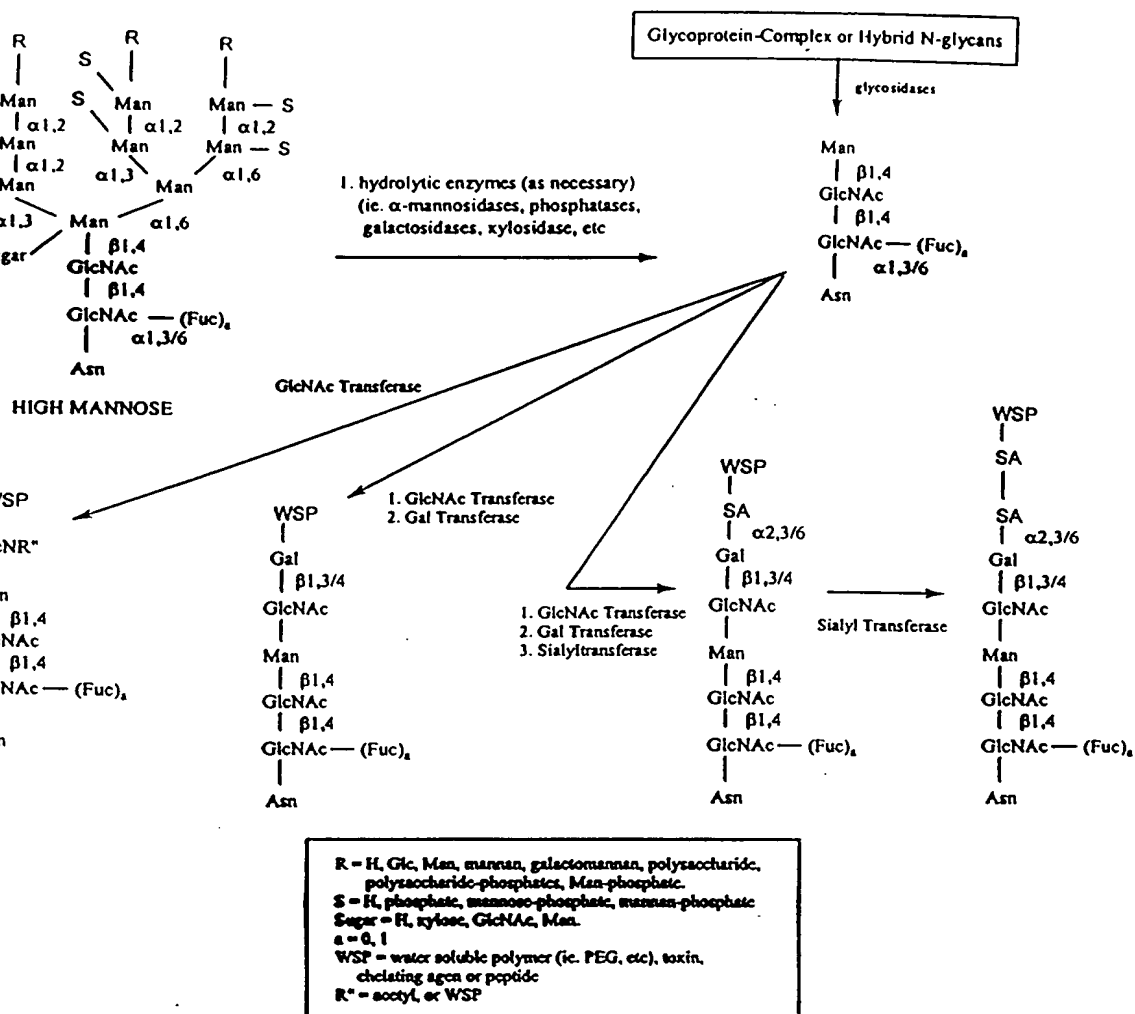
[illegible]

FIG. 2

Glycoprotein-Complex or Hybrid N-glycans

glycosidases

1. hydrolytic enzymes (as necessary)
(i.e. α and β -mannosidases, phosphatases,
galactosidases, xylosidase, etc)

HIGH MANNOSE

Gal transferase

Gal transferase;
sialyltransferase

Gal transferase;
sialyltransferase
sialyltransferase

Gal transferase;
fucosyltransferase

WSP

Gal

GlcNAc

GlcNAc — (Fuc)_a

Asn

WSP

SA

Gal

GlcNAc

GlcNAc — (Fuc)_a

Asn

WSP

SA

Gal

GlcNAc

GlcNAc — (Fuc)_a

Asn

WSP

Fuc

Gal

GlcNAc

GlcNAc — (Fuc)_a

Asn

Legend:

R = H, Glc, Man, mannan, galactomannan, polysaccharide,
polysaccharide-phosphates, Man-phosphate.

S = H, phosphate, mannose-phosphate, mannan-phosphate

Sugar = H, xylose, GlcNAc, Man.

a = 0, 1

WSP = water soluble polymer (i.e. PEG, etc), toxin,
chelating agen or peptide

R" = acetyl, or WSP

FIG. 3

Scheme 4.

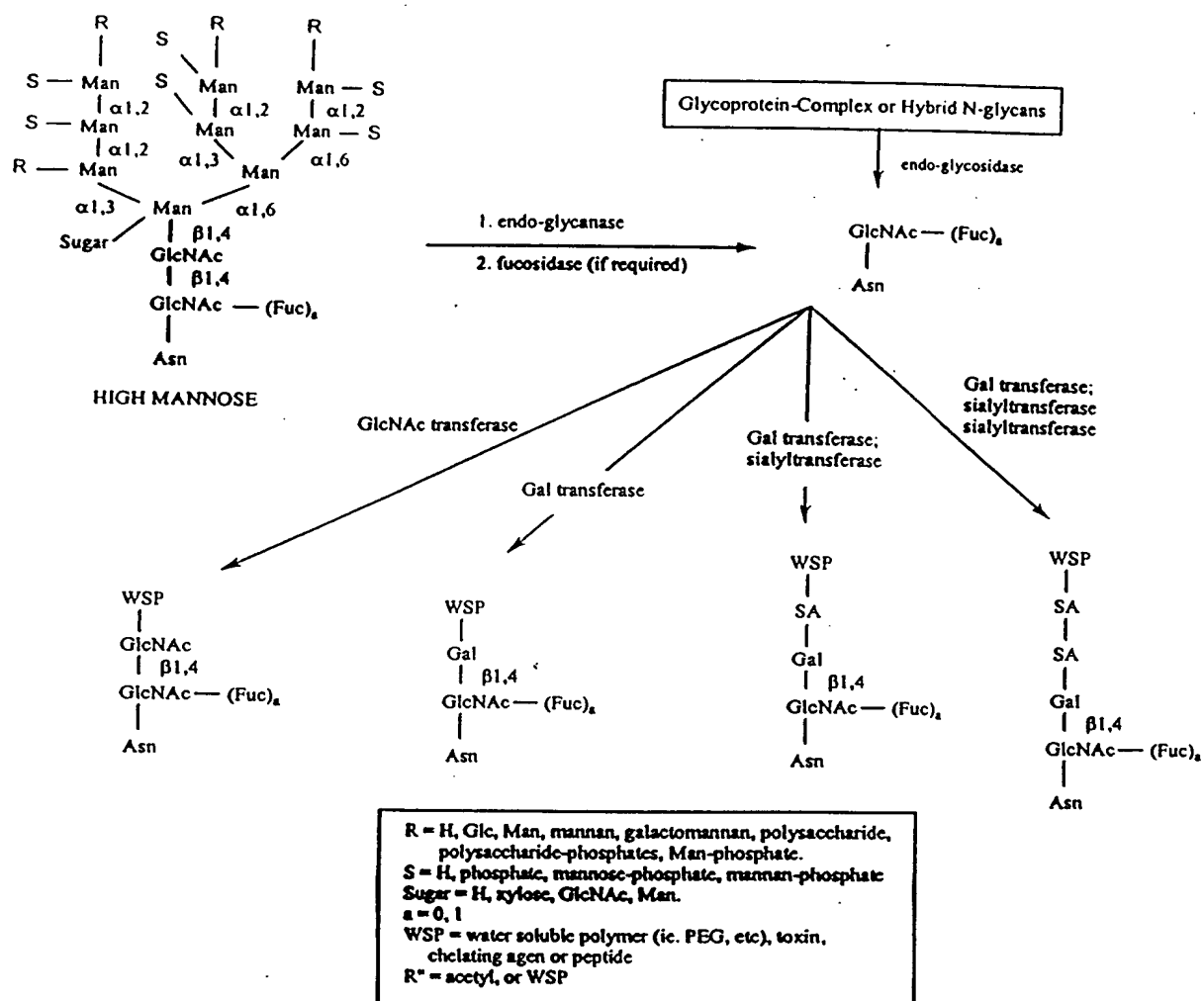


FIG. 4

Figure 5. N-linked Glycoprotein Structures.

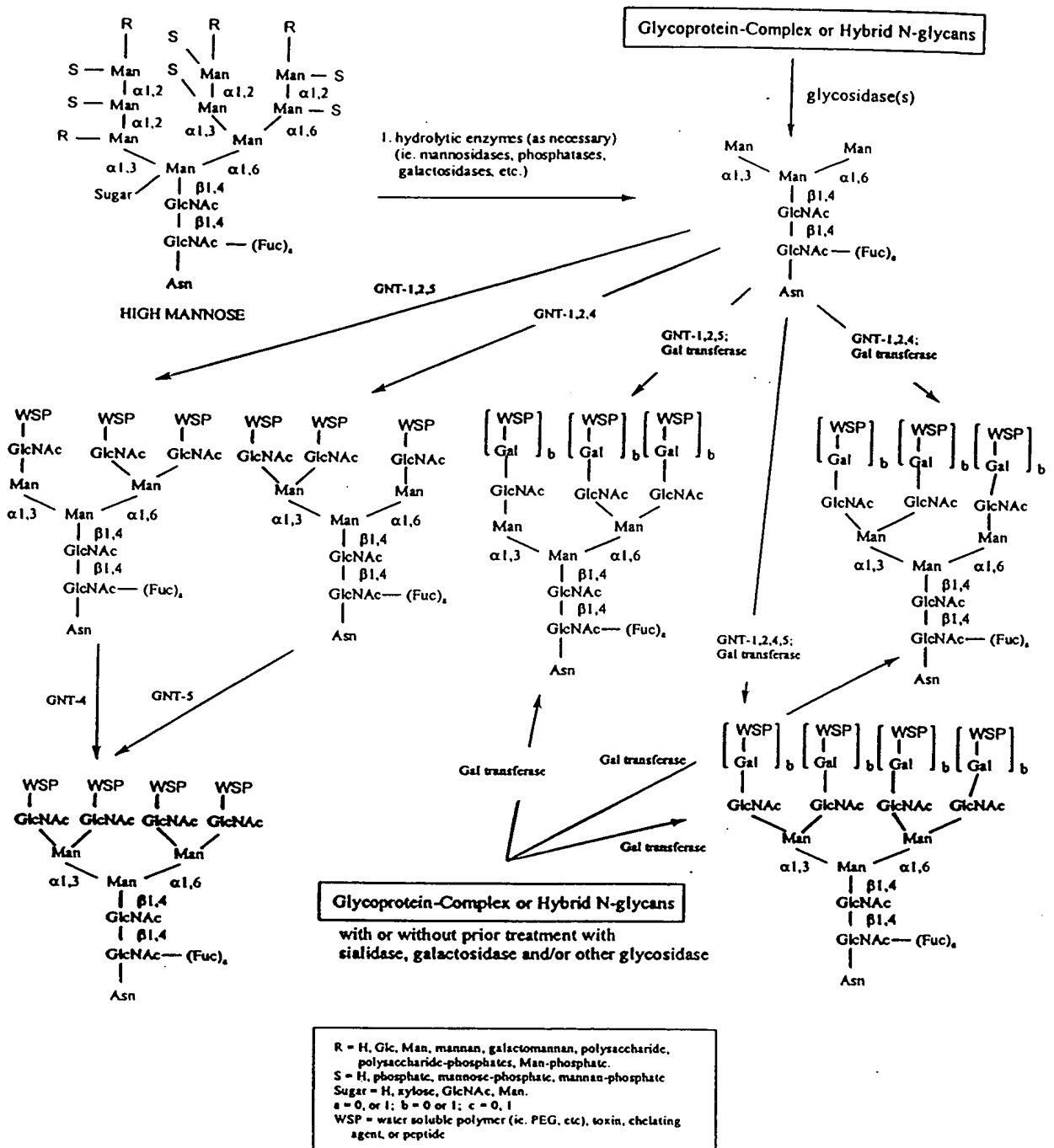


FIG. 5

The diagram illustrates the biosynthesis of N-glycans starting from a **Glycoprotein-Complex or Hybrid N-glycans**. The initial structure shows a core fucose (Fuc)₆ attached via β1,4 linkages to GlcNAc residues, which are further linked to mannose (Man) and galactose (Gal) residues. The process involves several enzymatic steps:

- I. hydrolytic enzymes (as necessary)** (ie. mannosidases, phosphatases, galactosidases, etc.) lead to the formation of **HIGH MANNOSE**.
- GNT-1,2,5; Gal transferase, sialyltransferase** leads to the formation of **Glycoprotein-Complex or Hybrid N-glycans** with or without prior treatment with sialidase, and/or other glycosidase.
- GNT-1,2,4; Gal transferase, sialyltransferase** leads to the formation of **Glycoprotein-Complex or Hybrid N-glycans** with or without prior treatment with sialidase, and/or other glycosidase.
- GNT-1,2,4,5; Gal transferase, sialyltransferase** leads to the formation of **Glycoprotein-Complex or Hybrid N-glycans** with or without prior treatment with sialidase, and/or other glycosidase.

The final structures show various branching patterns, including the addition of sialic acid (SA) residues and the presence of WSP (Watershed Sugar Polymer) groups. The diagram also includes a legend for abbreviations used in the structures:

- R = Mannan, galactomannan, polysaccharide, carbohydrate-phosphates, Man-phosphate.
- S = Sialic acid, mannose-phosphate, mannan-phosphate.
- Xylose, GlcNAc, Man.
- b = 0 or 1; c = 0, 1.
- or soluble polymer (ie. PEG, etc), toxin, chelating agent, peptide.

Figure 7. N-linked Glycoprotein Structures.

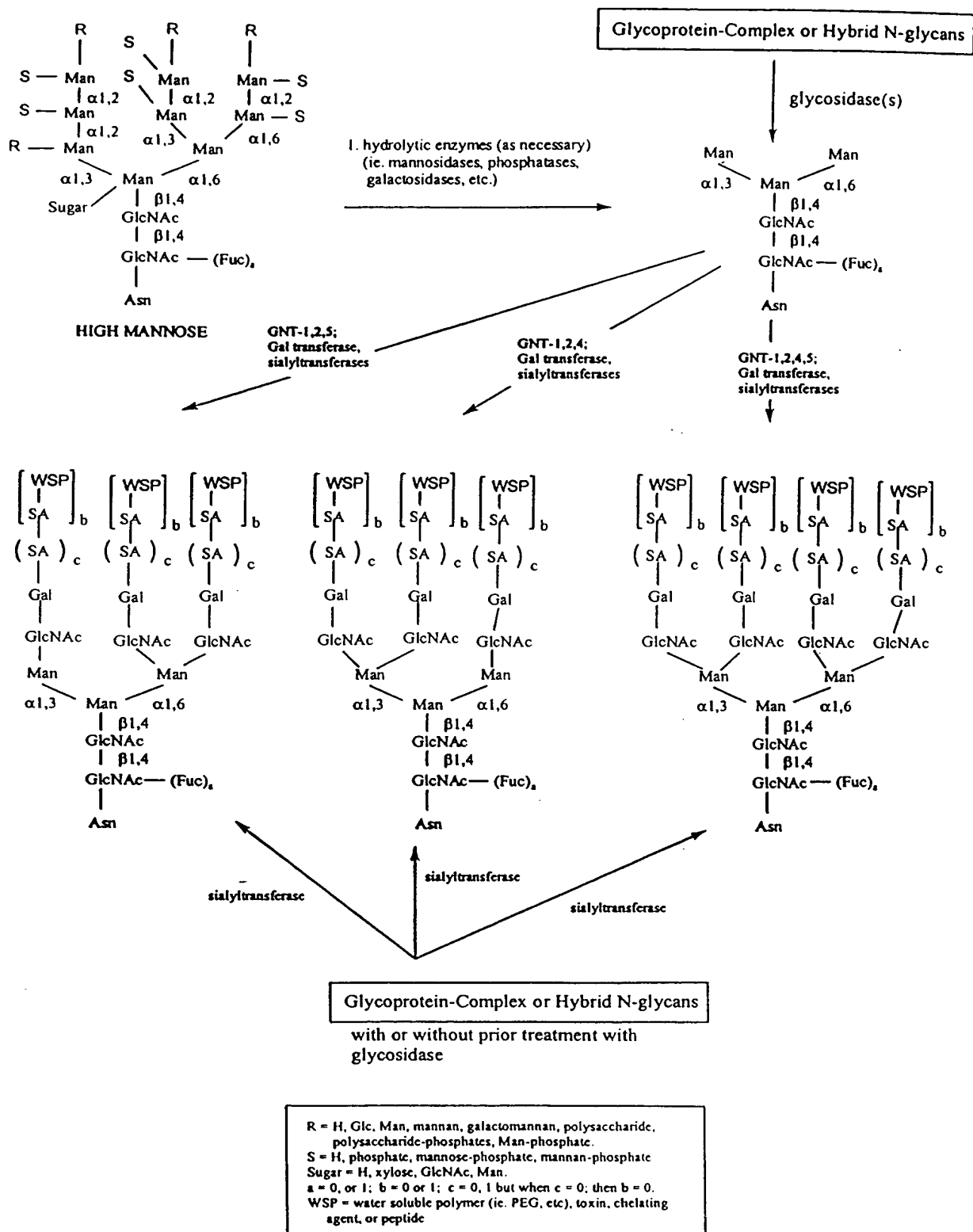


FIG. 7

[illegible]

FIG. 8

Scheme 9.

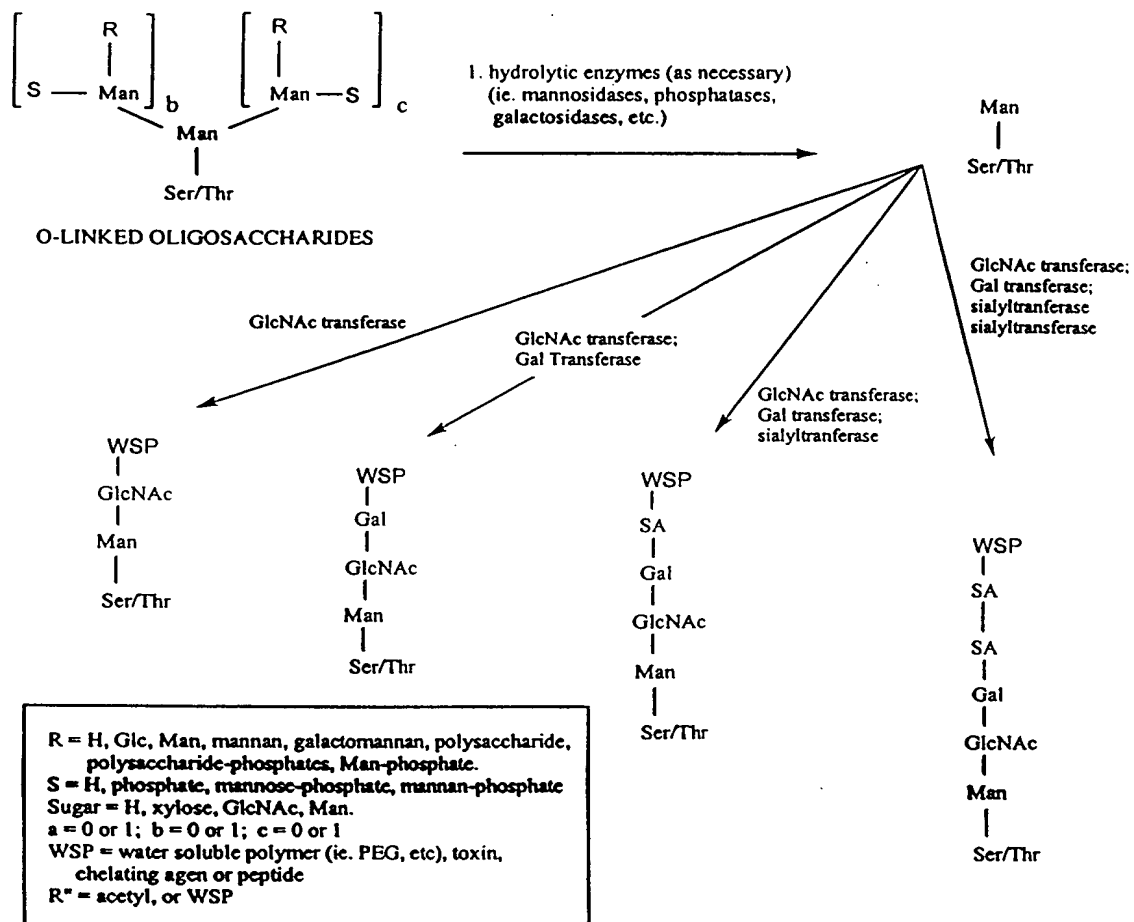


FIG. 9

R = H, Glc, Man, mann, galactomannan, polysaccharide, polysaccharide-phosphates, Man-phosphate.
S = H, phosphate, mannose-phosphate, mann-phosphate
Sugar = H, xylose, GlcNAc, Man.
a = 0 or 1; b = 0 or 1; c = 0 or 1
WSP = water soluble polymer (ie. PEG, etc), toxin, chelating agen or peptide
R' = acetyl, or WSP



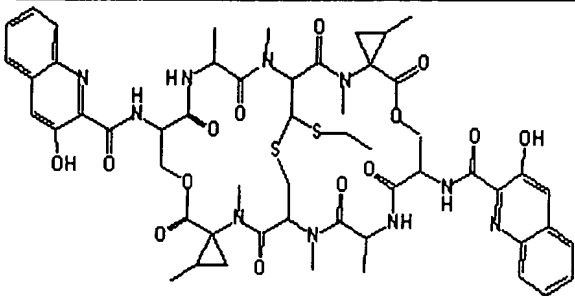
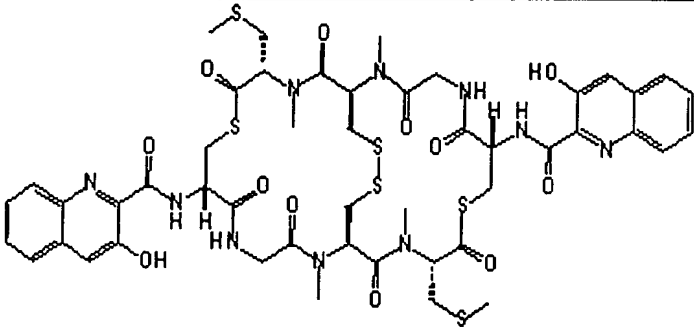
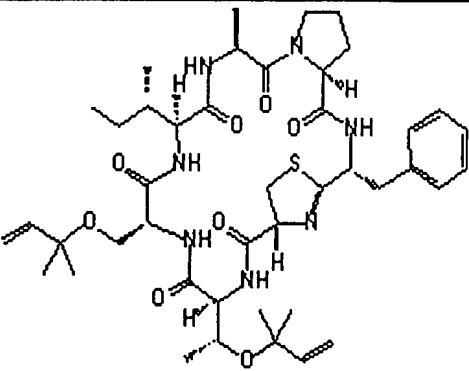
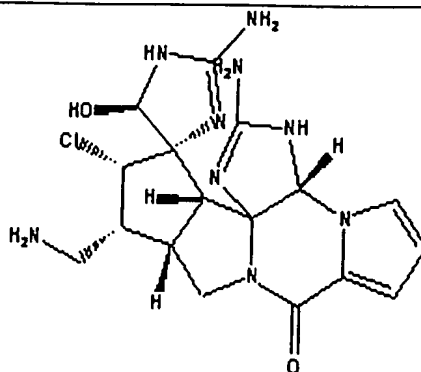
Chemical Structure				
Toxin Name/ Source/ Alternate ID	CAS RN / Analog	Indication/ Toxicity	Mechanism	Activity (IC ₅₀ nM); Tumor Type
				
	SW-163E/ <i>Streptomyces</i> sp SNA	Cancer and	not reported	0.3 P388
	15896/	Antibacterial/		0.2 A2780
	SW-163C;	low toxicity (mice ip)		0.4 KB
	SW-163A;			1.6 colon
SW-163B	SW-163B			1.3 HL-60
				
	Thiocoraline/ <i>Micromonospora marina</i> (actinomycete)	173046-02-1 Breast Cancer; Melanoma; Non-small lung cancer / not reported	DNA Polymerase alpha inhibitor (blocks cell progression from G1 to S)	lung, colon, CNS melanoma
				
	Trunkamide A ¹ / <i>Lissoclinum</i> sp (ascidian)	181758-83-8 Cancer/ not reported	not reported	cell culture (IC ₅₀ in micrograms/mL); 0.5 P388; 0.5 A549;

FIG. 11A

0.5 HT-29;
1.0 MEL-28

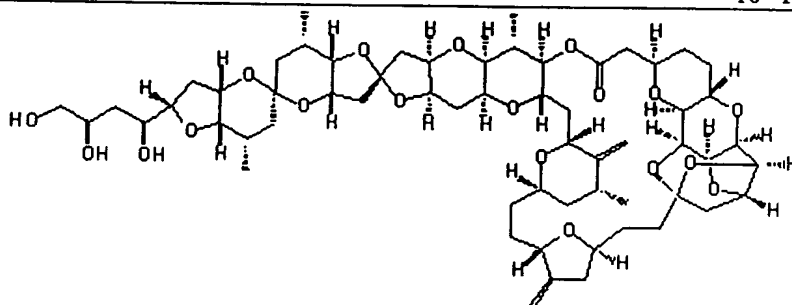


Palauamine²/
Stylorella agminata
(sponge)

148717-58-2

Lung cancer/
LD50 (i.p. in mice) is 13
mg/Kg

not reported cell culture (IC50 in
micrograms/mL);
0.1 P388
0.2 A549 (lung)
2 HT-29 (colon)
10 KB



Halichondrin B/
Halichondria Okadai,
Axinella Carteri and
Phanella carteri
(sponges)/
NSC-609385

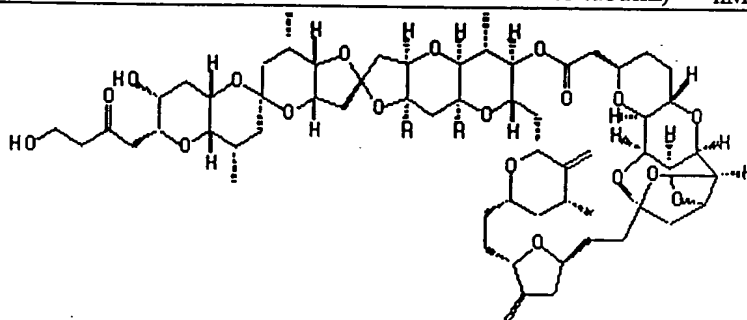
103614-76-2/

isohomohalic
hondrin B

cancer/
myelotoxicity dose
limiting (dogs, rats)

antitubulin;
cell cycle
inhibitor
(inhibits
GTP binding
to tubulin)

NCI tumor panel;
GI(50) from 50 nM to
0.1 nM;
LC50's from 40 μM to
0.1 nM (many 0.1 to 25
nM)



Isohomo-halichondrin B/
Halichondria Okadai,
Axinella Carteri and
Phanella carteri
(sponges)/
NSC-650467

157078-48-3/

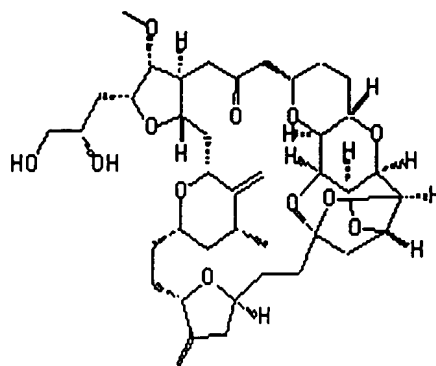
halichondrin
B

melanoma, lung, CNS,
colon, ovary/
not reported

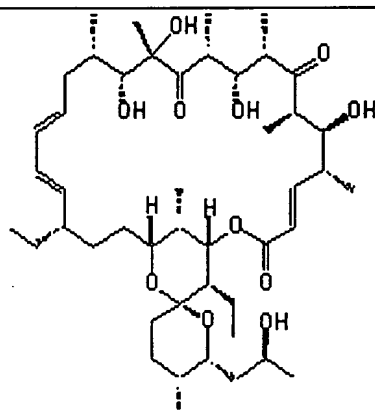
antitubulin;
cell cycle
inhibitor
(inhibits
GTP binding
to tubulin)

IC50's in 0.1 nM range
(NCI tumor panel)

FIG. 11B



Halichondrin B analogs/ semi-synthetic starting from <i>Halichondria</i> <i>Okadai</i> , <i>Axinell Carteri</i> and <i>Phanikell carteri</i> (sponges)/ ER-076349; ER-086526; B-1793; E-7389	253128-15-3/ ER-076349; ER-086526; B-1793; E-7389	solid tumors/ not reported	tubulin binding agent; disruption of mitotic spindles	cell culture (not reported); animal models active (tumor regression observed) in lymphoma, colon (multi-drug resistant).
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NK-130119/ <i>Streptomyces</i> <i>bottropensis/</i> NK-130119	132707-68-7	antifungal and anticancer/ not reported	not reported	25 ng/mL colon 8.5 ng/mL lung
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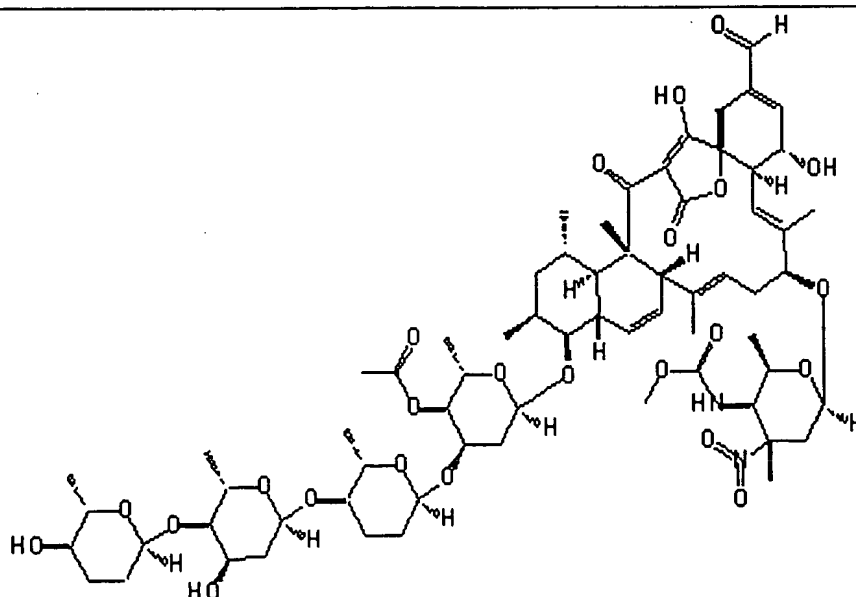
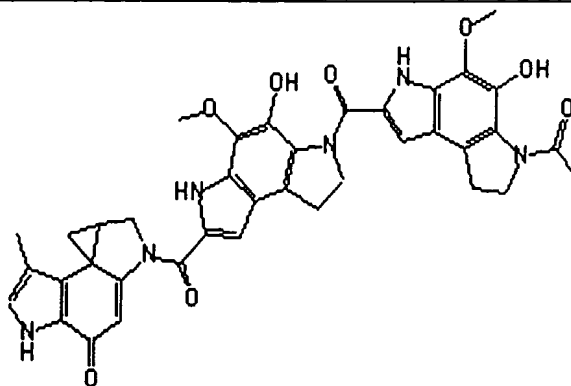
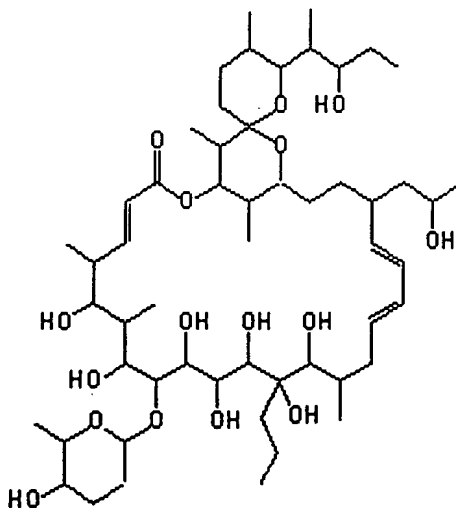


FIG. 11C

Tetrocarcin A/ not reported/ KF-67544	73666-84-9/ analogs are reported	cancer/ not reported	inhibits the anti- apoptotic function of Bcl2	not reported
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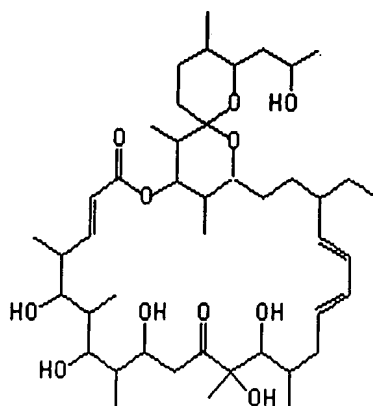


Gilvusmycin/ <i>Streptomyces</i> QM16	195052-09-6	cancer/ not reported	not reported	IC50's in ng/mL: 0.08 P388 0.86 K562 (CML) 0.72 A431 (EC) 0.75 MKN28 (GI); (for all < 1 nM)
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IB-96212/ marine actinomycete/ IB-96212	220858-11-7/ IB-96212; IB-98214; IB-97227	Cancer and Antibacterial/ not reported	not reported	IC50's in ng/mL: 0.1 P388
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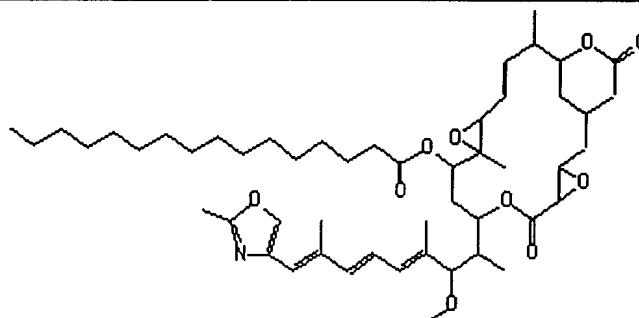
FIG. 11D



BE-56384³/
Streptomyces Sp./
BE-56384

207570-04-5 cancer/
not reported

not reported IC50's in ng/mL:
0.1 P388
0.29 colon 26
34 DLD-1
0.12 PC-13
0.12 MKM-45



Palmitoylrhizoxin/
semi-synthetic; *Rhizopus*
chinensis

135819-69-1/ cancer/
Analog of binds LDL; less
rhizoxin cytotoxic than rhizoxin

tubulin
binding
agent (cell
cycle
inhibitor)

not reported

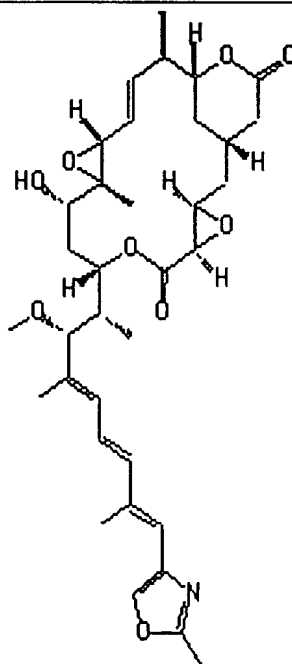
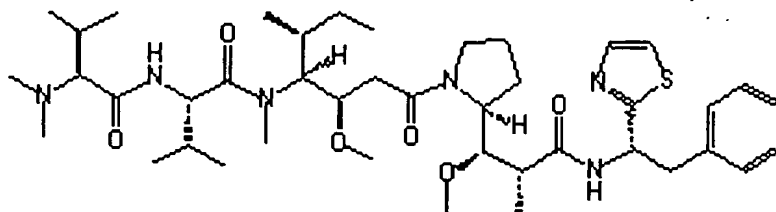
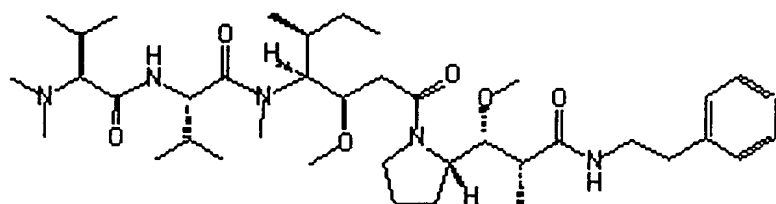


FIG. 11E

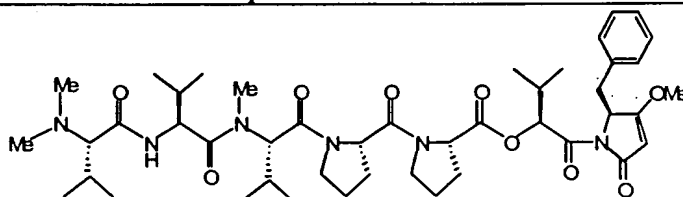
Rhizoxin/ <i>Rhizopus chinensis/</i> WF-1360; NSC-332598; FR-900216	95917-95-6; 90996-54-6	melanoma, lung, CNS, colon, ovary, renal, breast, head and neck/ Rapid Drug clearance; High AUC correlates with high toxicity	tubulin binding agent (cell cycle inhibitor)	NCI tumor panel (NSC 332598); log GI50's: 50 nM to 50 μ M; log LC50's: 50 μ M to 0.5 nM (several cell lines at 50 μ M).
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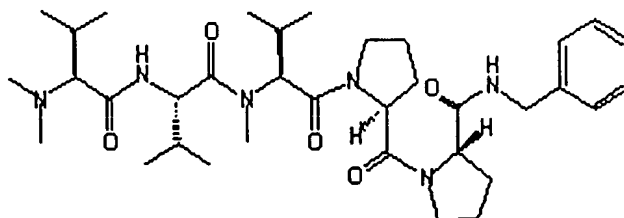
Dolastatin-10/ <i>Dolabella auricularia</i> (sea hare)/ NSC-376128	110417-88-4/ other Dolistatins (ie. 15) and analogues	prostate, melanoma, leukemia/ myelotoxicity (at greater than 0.3 pM)	tubulin binding (tubulin aggregation)	NCI tumor panel (60 cell line; GI50); 25 nM to 1 pM (most < 1 nM) (three cell lines μ M)
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soblidotin/ synthetic/ TZT-1027; auristatin PE	149606-27-9/ analogues prepared	cancer (pancreas, esophageal colon, breast, lung, etc) / MTD was 1.8 mg/Kg (IV); toxicity not reported	tubulin binding agent	cell culture: colon, melanoma, M5076 tumors, P388 with 75- 85% inhibition (dose not reported)
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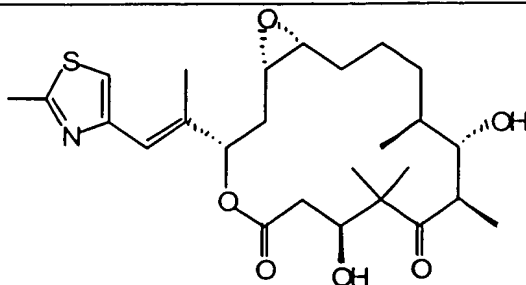
Dolastatin-15/ <i>Dolabella auricularia</i> (sea hare)	not reported/ other Dolistatins (ie. 15) and analogues	cancer/ not reported	Tubulin binding (tubuline aggregation)	NCI tumor panel (60 cell line; GI50); 25 nM to 39 pM (most < 1 nM) (one cell line 2.5 μ M); most active in breast
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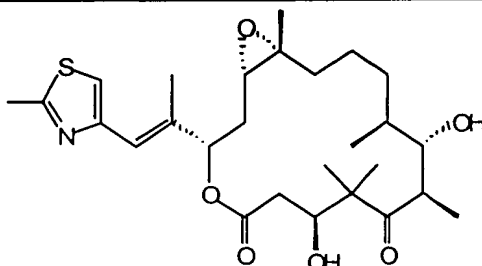
Cemadotin⁴/	1159776-69-	melanoma/	tubulin	NCI tumor panel (NCS
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FIG. 11F

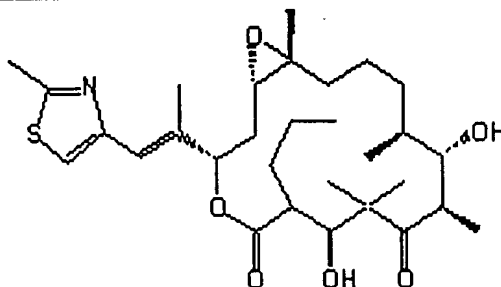
<p>Synthetic; Parent Dolastatin-15 was isolated from <i>Dolabella auricularia</i> (sea hare)/ LU-103793; NSC D-669356</p>	<p>9/ many analogs</p>	<p>hypertension, myocardial ischemia and myelosuppression were dose-limiting toxicities.</p>	<p>binding (tubulin aggregation) D-669356); active in breast, ovary, endometrial, sarcomas and drug resistant cell lines. Data not public.</p>
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<p>Epothilone A/ Synthetic or isolated from <i>Sorangium cellulosum</i> (myxococcales) strain So ce90)</p>	<p>not reported/ many analogs</p>	<p>cancer/ not reported</p>	<p>tubulin binding (tubulin polymerization)</p>	<p>IC50's of; 1.5 nM MCF-7 (breast) 27.1 nM MCF-7/ADR 2.1 nM KB-31 (melanoma) 3.2 nM HCT-116</p>
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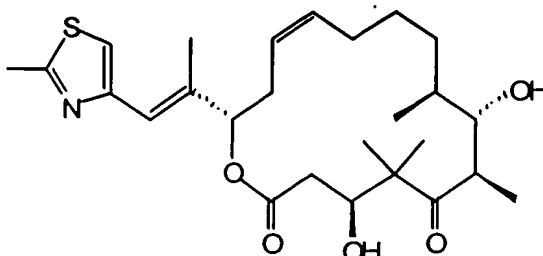


<p>Epothilone B/ Synthetic or isolated from <i>Sorangium cellulosum</i> (myxococcales) strain So ce90) / EPO-906</p>	<p>152044054-7/ many analogs</p>	<p>Solid tumors (breast, ovarian, etc)/ well tolerated; t1/2 of 2.5 hrs; partial responses (phase I); diarrhea major side effect.</p>	<p>tubulin binding (tubulin polymerization)</p>	<p>IC50's of; 0.18 nM MCF-7 (breast) 2.92 nM MCF-7/ADR 0.19 nM KB-31 (melanoma) 0.42 nM HCT-116; broad activity reported</p>
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<p>Epothilone Analog / Synthetic or semi-synthetic; Original lead, Epothilone A, isolated from <i>Sorangium cellulosum</i> (myxococcales) strain So ce90)/ ZK-EPO</p>	<p>not reported / hundreds of analog</p>	<p>cancer/ not reported</p>	<p>tubulin binding (tubulin polymerization)</p>	<p>IC50's of 0.30 to 1.80 nM in various tumor cell lines; active in drug resistant cell lines</p>
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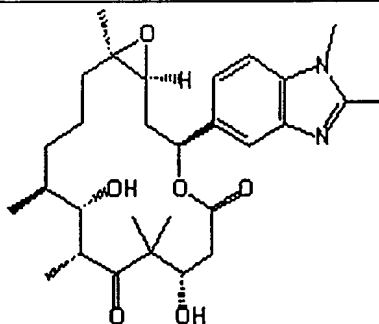
FIG. 11G



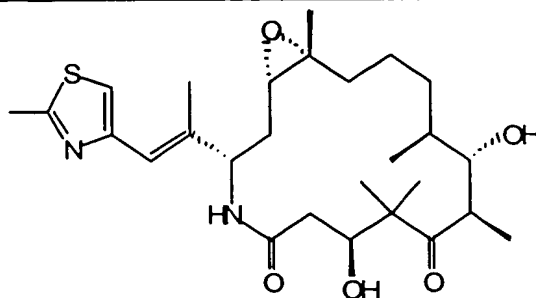
Epothilone D / Epothilone D, isolated from <i>Sorangium</i> <i>cellulosum</i> (myxococcales) strain So ce90)/ KOS-862	189452-10-9/ many analogs	Solid tumors (breast, ovarian, etc)/ emesis and anemia; t1/2 of 5-10 hrs.	tubulin binding (tubulin polymeriza- tion)	NCI tumor panel (NSC- 703147; IC50); 0.19 nM KB-31 (melanoma) 0.42 nM HCT-116; broad activity reported
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Structure Not Identified

Epothilone D analog ⁵/ Synthetic or semi- synthetic; Original lead, Epothilone D, isolated from <i>Sorangium</i> <i>cellulosum</i> (myxococcales) strain So ce90)/ KOS-166-24	189453-10-9/ hundreds of analogues	Solid tumors; not reported	tubulin binding (tubulin polymeriza- tion)	not reported
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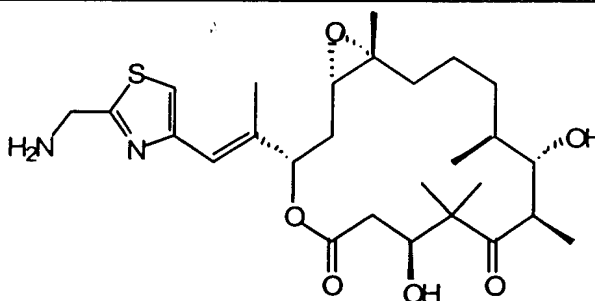
Epothilone Analog / Synthetic; Original lead, Epothilone A, isolated from <i>Sorangium</i> <i>cellulosum</i> (myxococcales) strain So ce90)/ CGP-85715	not reported/ hundreds of analogues	cancer; not reported	tubulin binding (tubulin polymeriza- tion)	not reported
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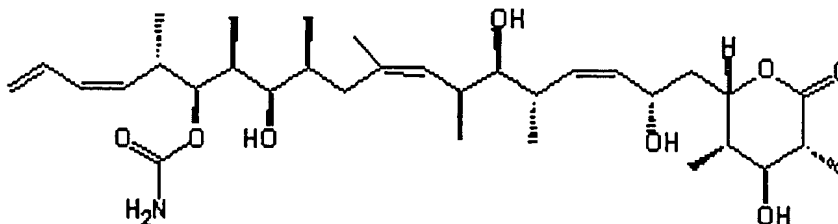
Epothilone Analog/	219989-84-1/	non-small cell Lung,	tubulin	NCI tumor Panel (NSC-
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FIG. 11H

Synthetic or semi-synthetic; Original lead, Epothilone B, isolated from <i>Sorangium cellulosum</i> (myxococcales) strain So ce90)/ BMS-247550	hundreds of analogs	breast, stomach tumor (objective responses in breast ovarian and lung)/ sever toxicity (fatigue, anorexia, nauseas, vomiting, neuropathy myalgia)	binding (tubulin polymerization)	710428 & NSC-710468); 8-32 nM (NCI data not available)
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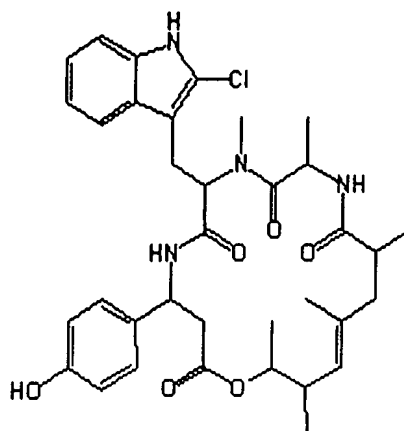


Epothilone Analog / Synthetic or semi-synthetic; Original lead, Epothilone B, isolated from <i>Sorangium cellulosum</i> (myxococcales) strain So ce90)/ BMS-310705	not reported/ hundreds of analogs	advanced cancers/ adverse events (diarrhea, nausea, vomiting, fatigue, neutropenia); t1/2 of 3.5 hrs; improved water solubility to BMS 247550.	tubulin binding (tubulin polymerization)	broad activity with IC50's of 0.7 to 10 nM
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Discodermolide / synthetic; originally isolated from <i>Discodermia dissoluta</i> (deep water sponge); rare compound (7 mg per 0.5 Kg sponge/ XAA-296	127943-53-7/ analog less potent	solid tumors/ not reported; 100-fold increase in water solubility over taxol	tubulin stabilizing agent (similar to taxol)	Broad activity (A549-nsclung, prostate, P388, ovarian with IC50's about 10 nM) including multi-drug resistant cell lines;
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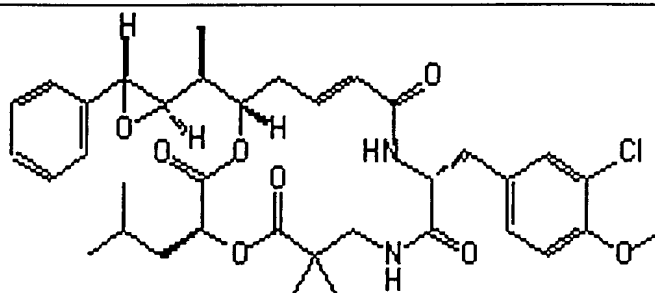
FIG. 11I



Chondramide D/
not reported

172430-63-6 cancer/
not reported

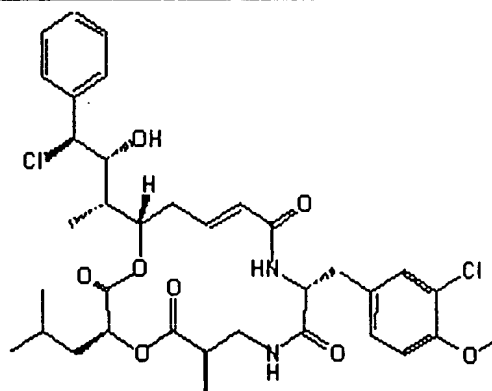
tubulin
binding
agent; actin
polymeriza-
tion inhibitor 5 nM A-549
(epidermoid carcinoma)
15 nM A-498 (kidney)
14 nM A549 (lung)
5 nM SK-OV-3 (ovary)
3 nM U-937
(lymphoma)



Cryptophycin analogs
(including 52, 55 and
others)^{6/}
Nostoc sp GSV 224 (blue-
green algae) isolated
Cryptophycin 1./
LY-355703; Ly-355702;
NSC-667642

204990-60-3 and 186256-
67-7/ many potent
analogs prepared at
Lilly
solid tumors, colon
cancer/
Phase II studies halted
because of severe
toxicity with one death
resulting from drug;

tubulin
polymeriza-
tion inhibitor broad activity (lung,
breast, colon, leukemia)
with IC50's of 2 to 40
pM; active against
multi-drug resistance
cell lines (resistant to
MDR pump). NCI
tumor panel, GI50's
from 100 nM to 10 pM;
LC50's from 100 nM to
25 pM.



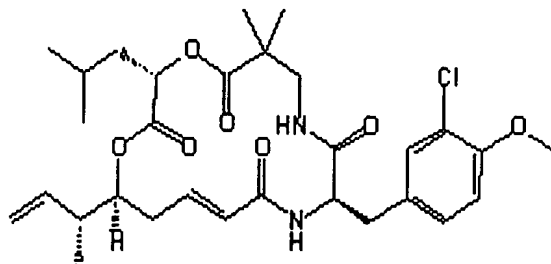
Cryptophycin 8/

168482-36-8; solid tumors/

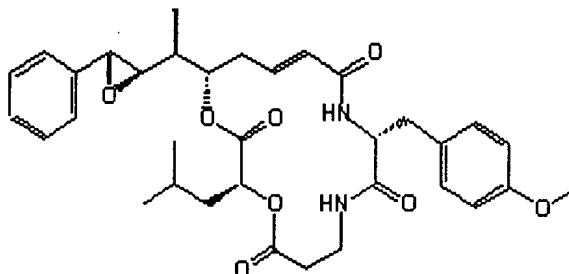
tubulin broad spectrum

FIG. 11J

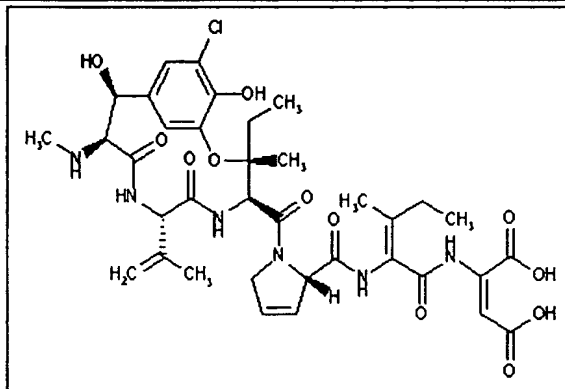
semi-synthetic; starting material from <i>Nostoc</i> sp.	168482-40-4; not reported 18665-94-1; 124689-65-2; 125546-14-7/ cryptophycin 5, 15 and 35	polymeriza- tion inhibitor	anticancer activity (cell culture) including multi-drug resistant tumors
--	--	-------------------------------	--



Cryptophycin analogs⁷ / synthetic; semi-synthetic, starting material from <i>Nostoc</i> sp./ LY-404291	219660-54-5/ LY-404292	solid tumors/ not reported	topoisomer- ase inhibitors	not reported
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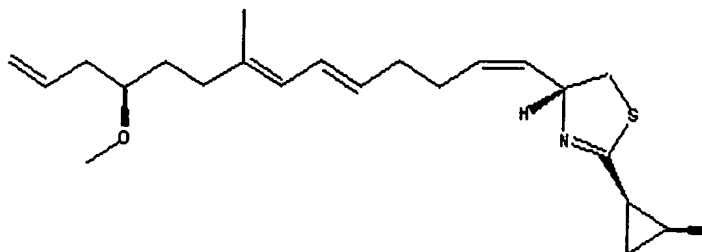


Arenastatin A analogs⁸ / <i>Dysidea arenaria</i> (marine sponge)/ Cryptophycin B; NSC- 670038	not reported/ analog prepared	cancer/ not reported	inhibits tubulin polymeriza- tion	8.7 nM (5 pg/mL) KB (nasopharyngeal); NCI tumor panel (GI50's); 100 pM to 3 pM
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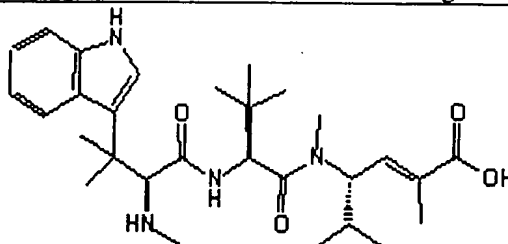


Phomopsin A / <i>Diaporthe toxicus</i> or <i>Phomopsis</i> <i>leptostromiformis</i> (fungi)	not reported	Liver cancer (not as potent in other cancers)/ not reported	tubulin binding agent	potent anticancer activity especially against liver cancer
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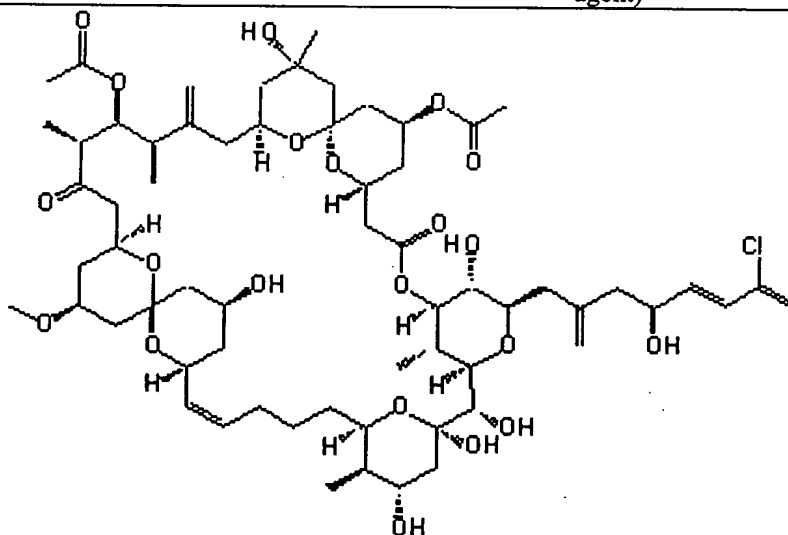
FIG. 11K



Curacin A and analogs/ <i>Lyngbya majuscula</i> (blue green cyanobacterium)	155233-30-0/ analogs have been prepared	Cancer/ not reported	Tubulin binding agent	broad activity (cancer cell lines); 1-29 nM
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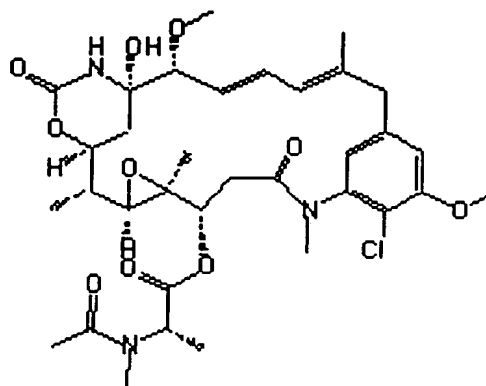


Hemiasterlins A & B and analogs⁹/ <i>Cymbastela</i> sp.	not reported/ criamide A & B; geodiamiolid- G	Cancer/ not reported	Antimitotic agent (tubulin binding agent)	broad activity: 0.3-3 nM MCF7 (breast); 0.4 ng/mL P388
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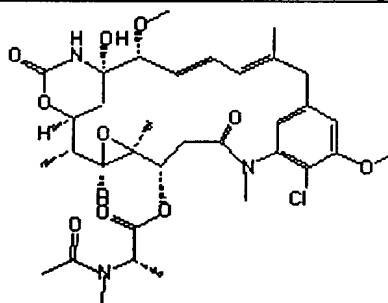


Spongistatins (1-9)¹⁰/ <i>Spirastrell spinispirulifera</i> (sea sponge)	149715-96-8; 158734-18-0; 158681-42-6; 158080-65-0; 150642-07-2; 153698-80-7; 153745-94-9; 150624-44-5; 158734-19-1/ other spongistatins	cancer/ not reported	tubulin binding agent	Most potent compounds ever tested in NCI panel cell line (mean GI50's of 0.1 nM; Spongistatin-1 GI50's of 0.025-0.035 nM with extremely potent activity against a subset of highly chemoresistant tumor types
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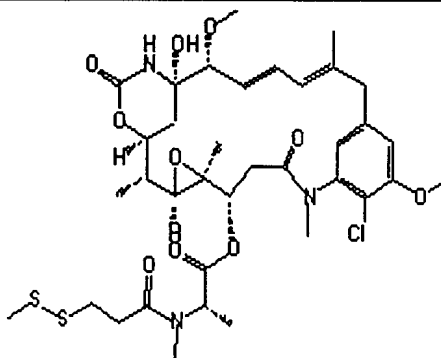
FIG. 11L



Maytansine/ <i>Maytenus</i> sp./ NSC-153858	35846-53-8/ other related macrolides	cancer/ severe toxicity	tubulin binding agent (causes extensive disassembly of the microtubule and totally prevents tubulin spiralization)	Broad Activity in NCI tumor panel (NSC- 153858; NSC-153858); NCI tumor panel, GI50's from 3 μ M to 0.1 pM; LC50's from 250 μ M to 10 pM. Two different experiments gave very different potencies.
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Maytansine-IgG(EGFR directed)-conjugate¹¹/ semi-synthetic; starting material from <i>Maytenus</i> sp.	not reported/ other related macrolides	breast , head and neck, Squamous cell carcinoma/ not reported	EGFR binding and tubulin binding	not reported
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Maytansine-IgG(CD56 antigen)-conjugate¹², 3.5 drug molecules per IgG/ semi-synthetic; starting material from <i>Maytenus</i>	not reported/ other related macrolides	Neuroendocrine, small- cell lung, carcinoma/ mild toxicity (fatigue, nausea, headaches and mild peripheral	CD56 binding and tubulin binding	antigen-specific cytotoxicity (cell culture; epidermal, breast, renal ovarian colon) with IC50's of
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FIG. 11M

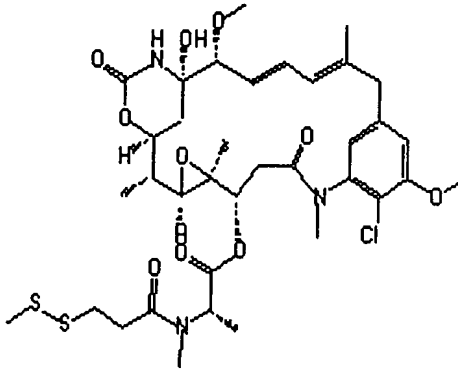
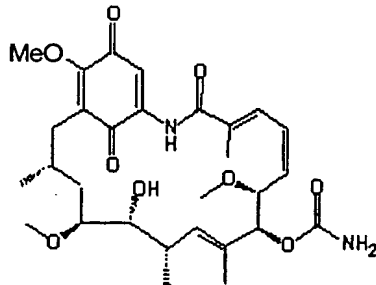
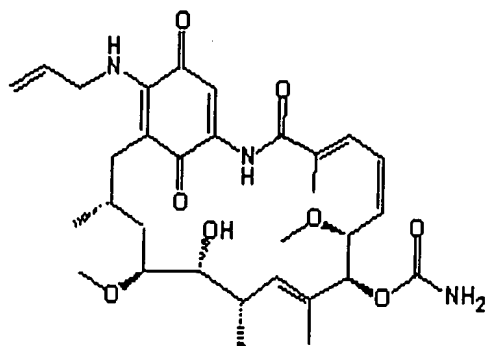
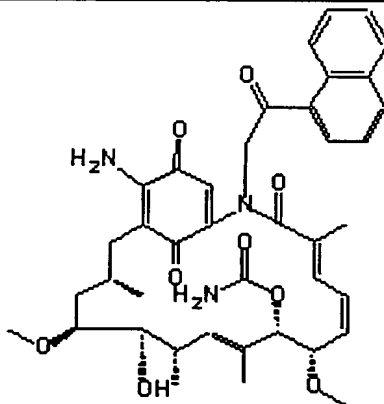
sp./ huN901-DM1		neuropathy); no hematological toxicity; MTD 60 mg/Kg, I.V., weekly for 4 weeks; only stable disease reported (humans)		10-40 pM; animal studies (miceSCLC tumor--alone and in combination with taxol or cisplatin completely eliminated tumors).
				
Maytansine-IgG(CEA antigen)-conjugate¹³ , 4 drug molecules per IgG/ semi-synthetic; starting material from <i>Maytenus</i> sp./ C424-DM1	not reported/ other related macrolides	non-small-cell lung, carcinoma pancreas, lung, colon/ mild toxicity (fatigue, nausea, headaches and mild peripheral neuropathy); pancreatic lipase elevated; MTD 88 mg/Kg, I.V., every 21 days; only stable disease reported (humans); t1/2 was 44 hr.	CEA binding and tubulin binding	antigen-specific cytotoxicity (cell culture; epidermal, breast, renal ovarian colon) with IC50's of 10-40 pM; animal studies (mice: melanoma [COLO- 205]--alone and in combination with taxol or cisplatin completely eliminated tumors);
				
Geldanamycin / <i>Streptomyces</i> <i>hygroscopicus</i> var. <i>Geldanus</i> / NSC-212518; Antibiotic U 29135; NSC-122750	30562-34-6/ natural derivatives	cancer/ not reported	binds Hsp 90 chaperone and inhibits function	NCI tumor panel (cell culture); 5.3 to 100 nM; most active in colon, lung and leukemia. NCI tumor panel, GI50's from 10 μM to 0.1 nM; LC50's from 100 μM to 100 nM. Two assays with very different potencies.

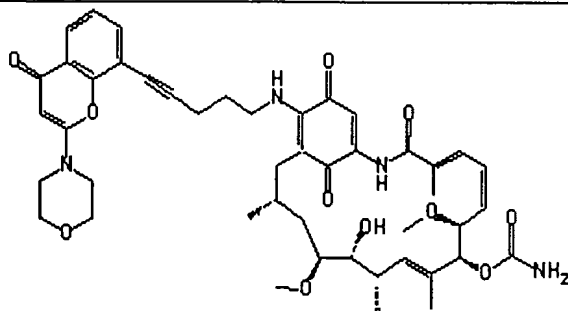
FIG. 11N



Geldanamycin Analog/ semi-synthetic; / CP-127374; 17-AAG; NSC-330507	745747-14-7/ Kosan, NCI and UK looking for analogs with longer t1/2 and oral activity; analogs include: NSC- 255110; 682300; 683661; 683663.	solid tumors/ Dose limiting toxicities (anemia, anorexia, diarrhea, nausea and vomiting); t1/2 (i.v.) is about 90 min; no objective responses measured at 88 mg/Kg (i.v. daily for 5 days, every 21 days);	binds Hsp 90 chaperone and inhibits function	cell culture (not reported); animal models active (tumor regression observed) in breast, ovary, melanoma, colon.
--	---	---	---	---



Geldanamycin analog/ semi-synthetic; / CP-202567	not reported/ analogs prepared	solid tumors/ not reported	binds Hsp 90 chaperone and inhibits function	not reported
---	--------------------------------------	-------------------------------	---	--------------



Geldanamycin conjugates/ semi-synthetic; / LY-294002-GM; PI3K-1- GM	345232-44-2/ analogs prepared	breast/ not reported	binds Hsp 90 chaperone and inhibits function; binds and	cell culture (no reported); animal models performed
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FIG. 110

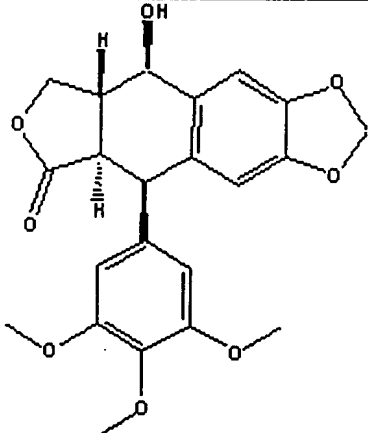
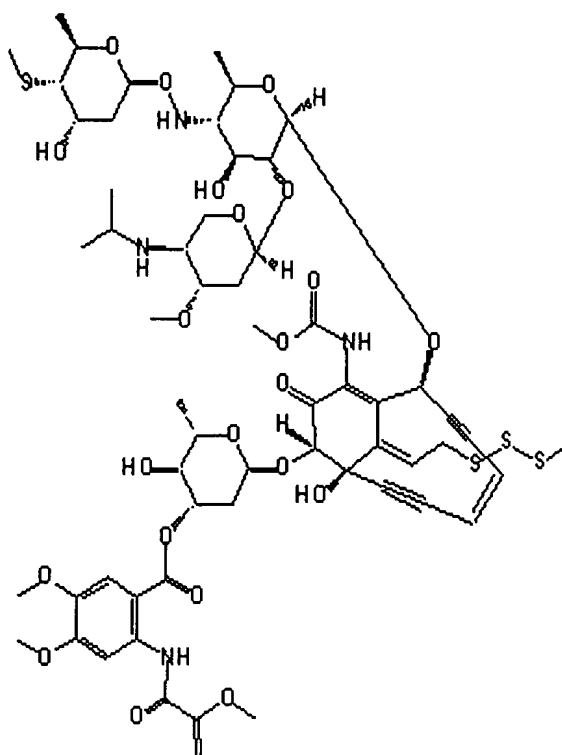
				inhibits PI-3 kinase
Structure Not Reported				
Geldanamycin Analog/ not reported/ CNF-101	not reported/ analogs prepared	breast, prostate/ not reported	binds Hsp 90 chaperone and inhibits function	not reported
Structure Not Reported				
Geldanamycin- testosterone conjugate/ semi-synthetic/ GMT-1	not reported/ analogs prepared	prostate/ not reported	binds Hsp 90 chaperone and inhibits function and testosterone receptors where it is internalized	not reported; conjugate has a 15-fold selective cytotoxicity for androgen positive prostate cells
				
Podophyllotoxin/ <i>Podophyllum</i> sp.	518-28-5/ many analogs	<i>Verruca vulgaris</i> , Condyloma/ severe toxicity when given i.v. or s.c.	tubulin inhibitor and topoisomer- ase inhibitor	broad activity (cell culture) with IC50's in μM range

FIG. 11P



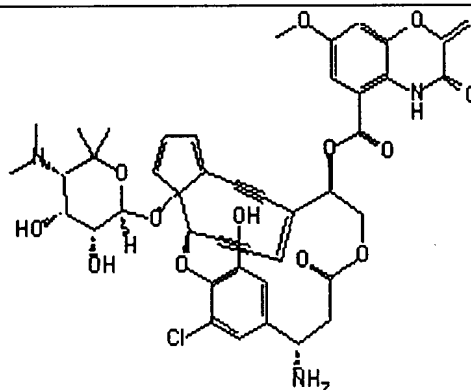
esperamicin-A1/
not known/
BBM-1675A1; BMY-
28175; GGM-1675

99674-26-7

cancer/
not reported (suspected
severe toxicity)

DNA
cleaving
agent

highly potent activity
(cell culture); animal
models highly potent
with optimal dose of
0.16 micrograms/Kg



C-1027¹⁴/
Streptomyces setonii C-
1027/
C-1027

120177-69-7

cancer (examined
hepatoma, breast, lung
and leukemia/
not reported

DNA
cleaving
agent

extremely potent (cell
culture) IC₅₀'s in pM
and fM; conjugated to
antibodies the potency
remains the same (ie.
5.5 to 42 pM);

FIG. 11Q

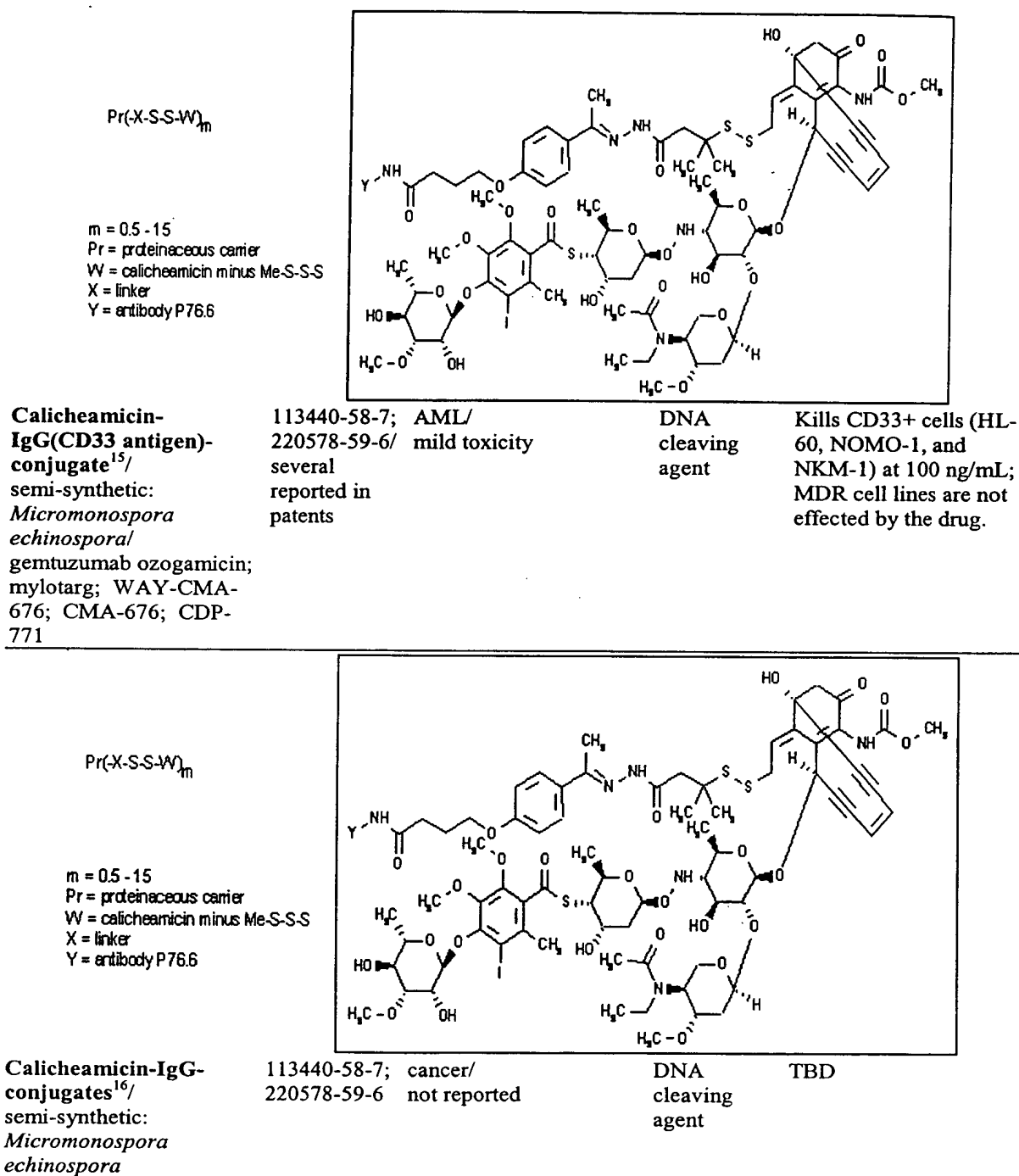
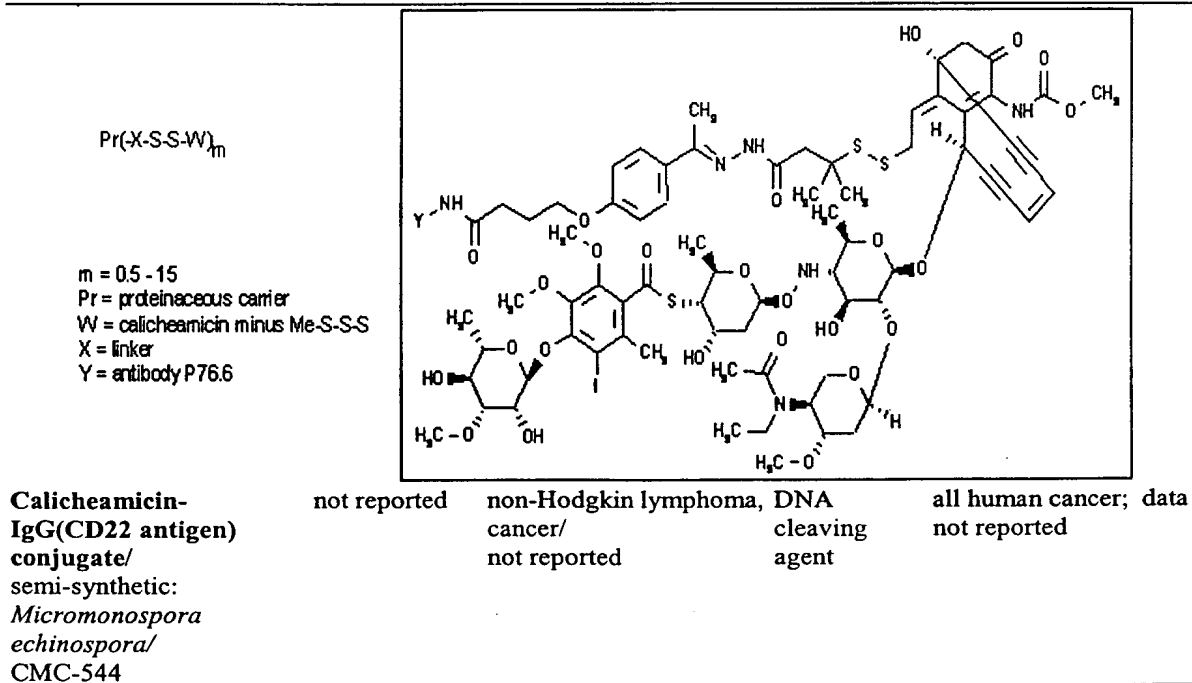
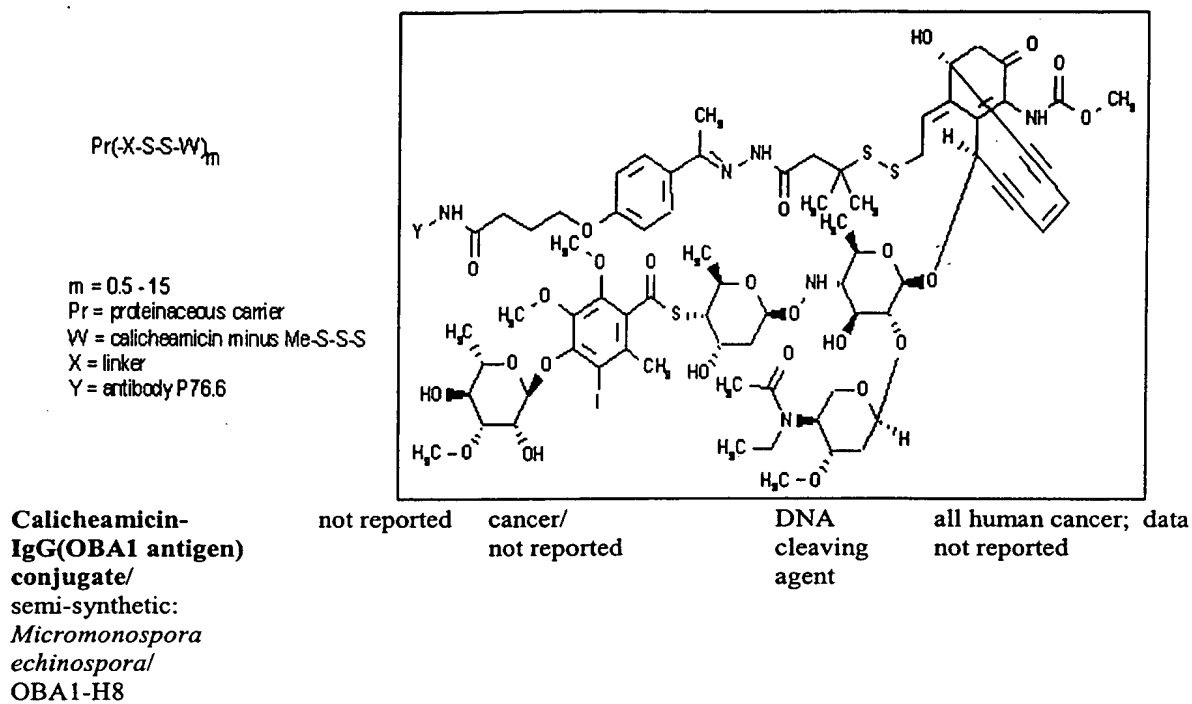


FIG. 11R



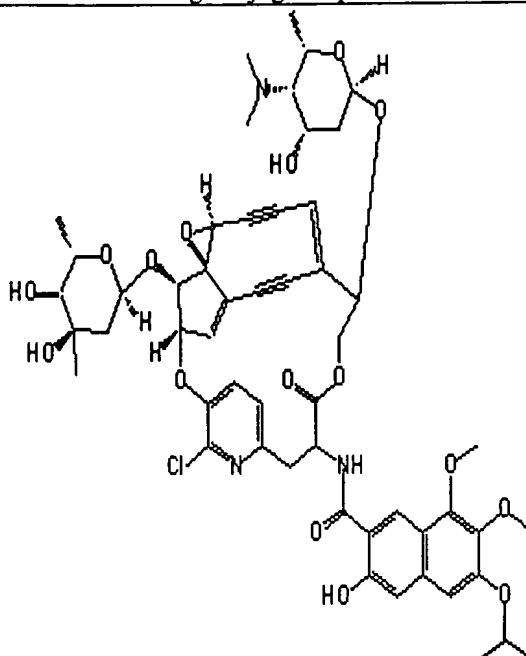
parially esterified polystyrene maleic acid copolymer (SMA)
 conjugated to neocarzinostatin (NCS)

Neocarzinostatin ^{17/} semi-synthetic; <i>Streptomyces carconistaticus/</i> Zinostatin stimalamer; YM-881; YM-16881	123760-07-6; 9014-02-2	liver cancer and brain cancer/ not reported	DNA cleaving agent	cell culture data not reported.
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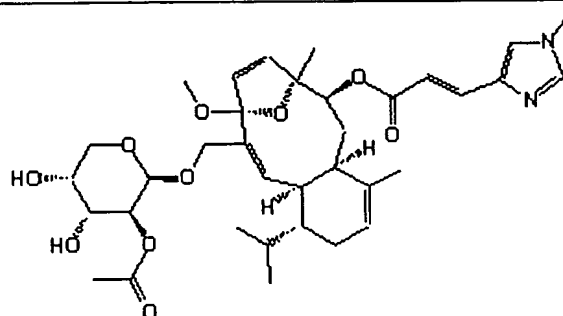
FIG. 11S

IgG (TES-23)-conjugated to neocarzinostatin

Neocarzinostatin/ not reported/ TES-23-NCS	not reported	solid tumors/ toxicity not reported; the TES-23 antibody (without anticancer agent) was as effective at eliminating tumors as the drug conjugated protein	DNA cleaving agent and immunostim- ulator	cell culture data not reported.
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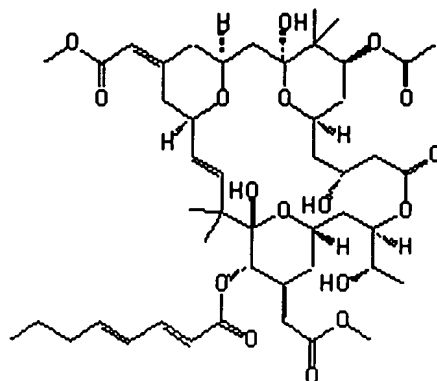


Kedarcidin ¹⁸ / <i>Streptoalloteichus</i> sp NOV strain L5856, ATCC 53650/ NSC-646276	128512-40-3; 128512-39-0/ chromophore and protein conjugate	cancer/ not reported	DNA cleaving agent	cell culture (IC50's in ng/mL), 0.4 HCT116; 0.3 HCT116/VP35; 0.3 HCT116/VM46; 0.2 A2780; 1.3 A2780/DDP. animal models in P388 and B-16 melanoma. NCI tumor panel, GI50's from 50 μ M to 5 μ M.
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Eleutherobins/ marine coral	174545-76-7/ sarcodictyins (marine coral)	cancer/ not reported	tubulin binding agent	similar potency to taxol; not effective against MDR cell lines
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FIG. 11T

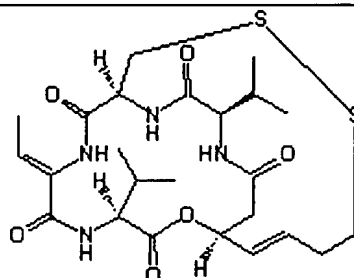


Bryostatin-1/
Bugula neritina (marine
 bryozoan)/
 GMY-45618; NSC-
 339555

83314-01-6

leukemia, melanoma,
 lung, cancer/
 myalgia; accumulated
 toxicity; poor water
 solubility; dose limiting
 toxicity

immunostim- not reported
 ulant (TNF,
 GMCSF,
 etc);
 enhances cell
 kill by
 current
 anticancer
 agents



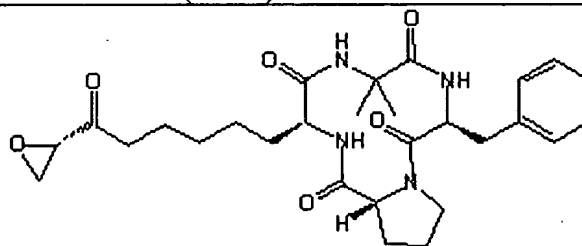
FR-901228/
Chromobacterium
violaceum strain 968/
 NSC-63-176; FK-228

128517-07-7

leukemia, T-cell
 lymphoma, cancer/
 toxic doses (LD50) 6.4
 and 10 mg/Kg, ip and iv
 respectively; GI
 toxicity, lymphoid
 atrophy; dose limiting
 toxicity (human) 18
 mg/Kg; t1/2 of 8 hrs
 (human)

histone
 deacetylase
 inhibitor

In vitro cell lines (NCI
 tumor panel);
 IC50's of between 0.56
 and 4.1 nM (breast,
 lung, gastric colon,
 leukemia)



Chlamydocin/
 not reported

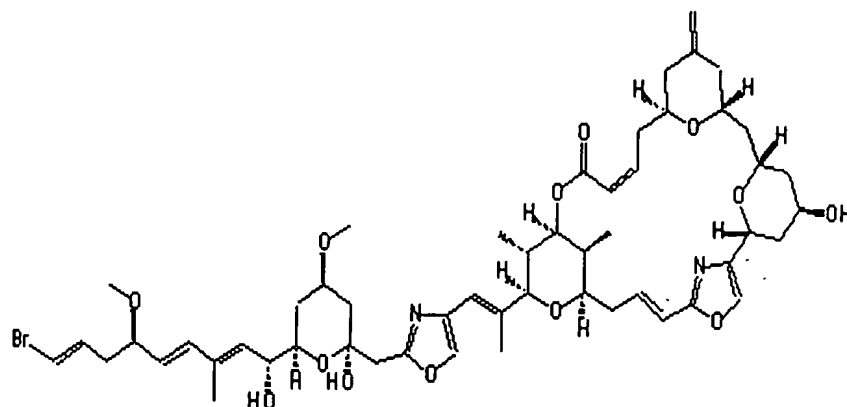
53342-16-8

cancer/
 not reported

histone
 deacetylase
 inhibitor

not reported (cell
 culture);
 inhibits histone
 deacetylase at an IC50
 of 1.3 nM

FIG. 11U

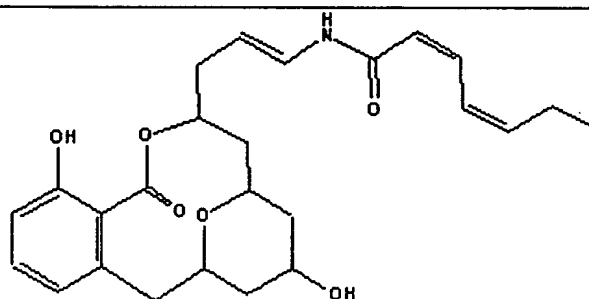


Phorboxazole A¹⁹/
marine sponge

181377-57-1; leukemia, myeloma/
165689-31-6; not reported
180911-82-4;
165883-76-1/
analogs
prepared

not reported
(induces
apoptosis)

NCI tumor panel
(details not reported);
IC50's of 1-10 nM. The
inhibition values
(clonogenic growth of
human cancer cells) at
10 nM ranged from 6.2
to > 99.9% against
NALM-6 human B-
lineage acute
lymphoblastic
leukemia cells, BT-20
breast cancer cells and
U373 glioblastoma
cells, with the specified
compound showing
inhibition values in the
range of 42.4 to >
99.9% against these cell
lines.; IC50's are nM
for MDR cell lines.



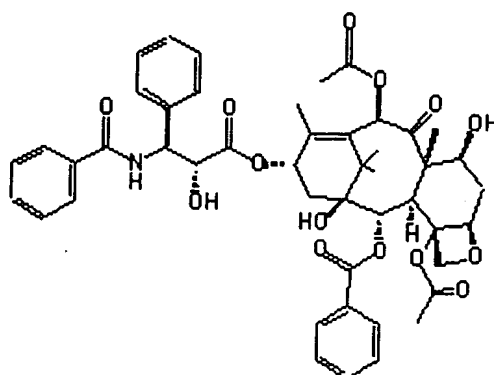
Apicularen A/
Chondromyces robustus

220757-06-2/ cancer/
natural not reported
derivatives

not reported

IC50's of 0.1 to 3
ng/mL (KB-3-A, KB-
Va, K562, HL60, U937,
A498, A549, PV3 and
SK-OV3)

FIG. 11V



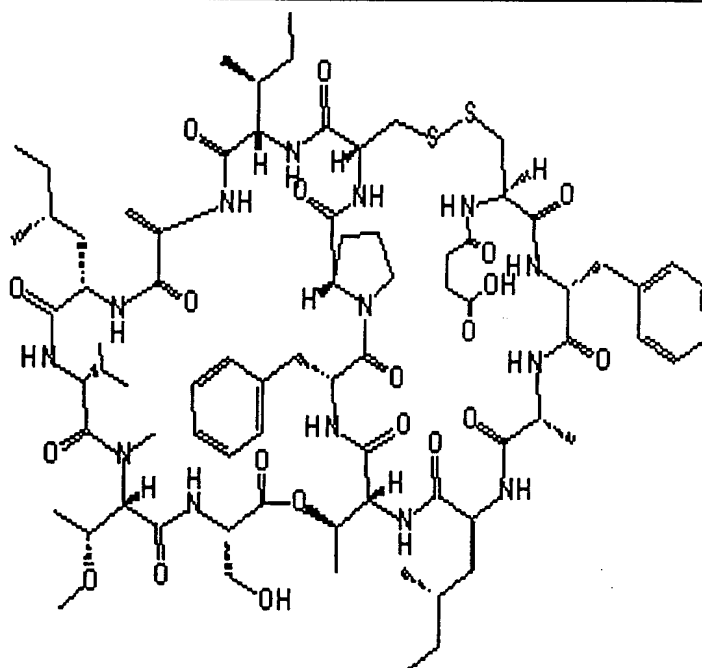
Taxol/
Pacific yew and fungi/
Paclitaxel; NSC-125973

33069624/
many analogs

cancer; breast, prostate,
ovary, colon, lung, head
& neck, etc./
severe toxicity (grade III
and IV)

tubulin
binding
agent

NCI tumor panel;
GI50's of 3 nM to 1
 μ M;
TGI 50 nM to 25 μ M



Vitilevuamide/
Didemnum cuculliferum
or *Polysyncraton*
lithostrotum

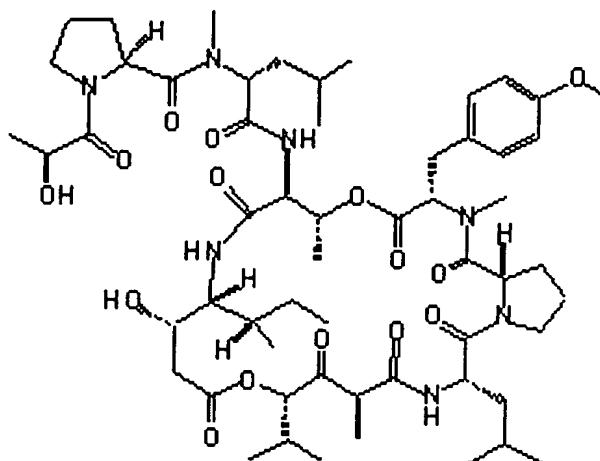
191681-63-7

cancer/
not reported

tubulin
binding
agent

cell culture; IC50's of
6-311 nM (panel of
tumor cell lines
HCT116 cells, A549
cells, SK-MEL-5 cells
A498 cells). The
increase in lifespan
(ILS) for CDF1 mice
after ip injection of
P388 tumor cells was in
the range of -45 to
+70% over the dose
range of 0.13 to 0.006
mg/kg.

FIG. 11W



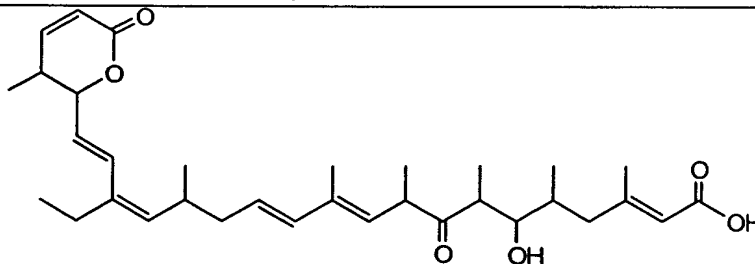
Didemnin B/
Trididemnum solidum/
 NSC-2325319; IND
 24505

77327-05-0;
 77327-04-9;
 77327-06-1/
 other related
 natural
 products

non-Hodgkin's
 lymphoma, breast,
 carcinoma, CNS, colon/
 Discontinued due to
 cardiotoxicity; nausea,
 neuro-muscular toxicity
 and vomiting MTD 6.3
 mg/Kg; toxicity
 prevented achieving a
 clinically signif. effect;
 rapidly cleared (t1/2 4.8
 hrs

inhibits
 protein
 synthesis via
 EF-1

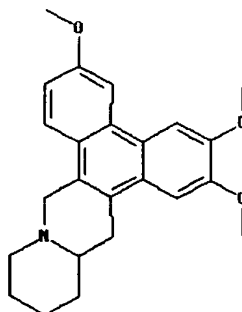
NCI 60-tumor panel
 (GI50's): 100 nM to 50
 fM.
 Not potent against
 MDR cell lines.



Leptomycin B/
Streptomyces sp. strain
 ATS 1287/
 NSC-364372; elactocin

87081-35-4

NCI 60-tumor panel
 (GI50's):
 8 μ M to 1 pM; (LC50):
 250 μ M to 10 nM
 (several cell lines at 0.1
 nM). Two testing
 results with very
 different potencies.



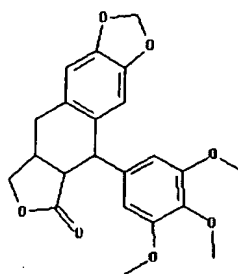
Cryptopleurin/

NCI 60-tumor panel

FIG. 11X

not known/
NSC-19912

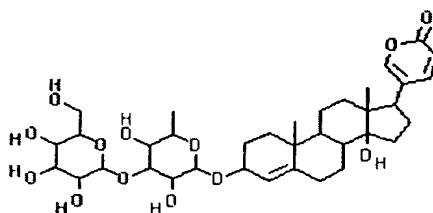
(GI50's): 19 nM to 1
pM; (LC50): 40 μ M to
10 nM (several cell
lines at 1 pM).



Silicicolin/
not known/
NSC-403148,
deoxypodophyllotoxin,
desoxypodophyllotoxin
podophyllotoxin,
deoxysilicicolin

19186-35-7

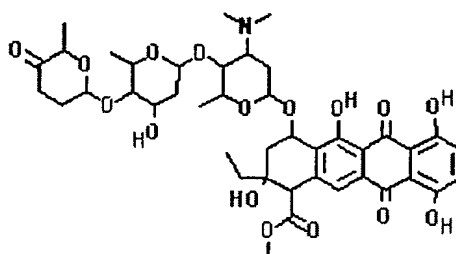
NCI 60-tumor panel
(GI50's): ~100 nM to 3
nM; (LC50): 50 μ M to
10 nM



Scillaren A/
not known/
NSC-7525; Gluco-
proscillaridin A;
Scillaren A

124-99-2

NCI 60-tumor panel
(GI50's): 50 nM to 0.1
nM;
(LC50): 250 μ M to 0.1
nM



Cinerubin A-HCl/
not known/
NSC-243022; Cinerubin
A hydrochloride;
CL 86-F2 HCl;
CL-86-F2-hydrochloride

not reported

NCI 60-tumor panel
(GI50's): 15 nM to 10
pM; (LC50): 100 μ M
to 6 nM

FIG. 11Y